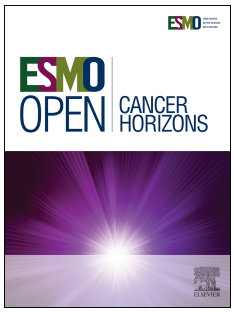
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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PII: S2059-7029(22)00044-8

DOI: https://doi.org/10.1016/j.esmoop.2022.100423

Reference: ESMOOP 100423

To appear in: *ESMO Open*

Received Date: 18 January 2022

Accepted Date: 1 February 2022

Please cite this article as: Kubelac P, Preda A, Ciuleanu T, Todor N, Balacescu O, Achimas-Cadariu P, Iancu D, Mocan C, Bandi-Vasilica M, Lupse M, Briciu VT, Man MA, Vlad C, Outcomes of patients with cancer infected with SARS-CoV-2: results from the Ion Chiricu□ă Oncology Institute series, *ESMO Open* (2022), doi: https://doi.org/10.1016/j.esmoop.2022.100423.

Outcomes of patients with cancer infected with SARS-CoV-2: results from the Ion Chiricuță Oncology Institute series

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Abstract

Background: The evolution of COVID-19 is a controversial topic in cancer patients. They have been designated by international organizations as a vulnerable population at greater risk for contracting SARS-CoV2 and having a more severe clinical outcome.

Patients and methods: Active screening at our Institution became routine early in the pandemic. We have examined the clinical data of 341 cancer patients, with a positive RT-PCR SARS-CoV2 test between April 2020 and February 2021, in the prevaccination era.

Results: During the infection, 40.5% remained asymptomatic, 27.6% developed a mild form, 20.5% had a moderate form, and 11.4% a severe-critical form of COVID-19 that led to death in 7.6% of cases. Treatment was adapted to disease severity according to National guidelines. In our series, the incidence of COVID-19 infection was lower in cancer patients compared to the general population ($p<0.001$), however, the mortality rate was higher in cancer patients in comparison to the general population (7.6% vs. 2.9%, $p<0.001$). The prognostic factors were assessed by three distinct univariate and multivariate analyses: a) evolution to a moderate or severe-critical clinical manifestation, b) clinical worsening (severe-critical form or death) and c) overall survival. In the multivariate analysis, the prognostic factors associated with the evolution to a moderate or severe-critical clinical manifestation were: PS (performance status) ($p<0.0001$) and no active treatment in the previous 3 months ($p=0.031$). Factors associated with clinical worsening were: PS ($p<0.0001$), peripheral arterial disease ($p=0.03$), and chronic liver disease ($p=0.04$). Factors associated with impaired overall survival were PS ($p<0.0001$), ischemic cardiac disease ($p=0.0126$), chronic liver disease ($p=0.001$), and radiotherapy ($p=0.0027$).

Conclusion: Our series confirms a more severe evolution for COVID-19 infection in cancer patients, with PS as the most prominent prognostic factor in all three multivariate analyses. By active screening, efforts should be in place to keep cancer units as Coronavirus-free sanctuaries

Keywords: cancer , prognostic factors , Covid-19 pandemic

Highlights

• This is the first comprehensive study addressing the impact of COVID-19 in a large cohort of cancer patients in Romania

• Oncological patients had a higher death rate after COVID-19 infection in comparison with the general population

• Decreased performance was the prominent prognostic factor correlated with worse outcomes and death in multiple multivariate analysis

INTRODUCTION

The COVID-19 pandemic posed significant problems for the Romanian health system, with 730,056 positive cases and 18,402 deaths recorded until 1 February 2021 and an acceleration trend of the second wave in October-November 2020 with a peak of 10,269 new cases recorded on 18 November 2020 (1).

The Oncology Institute "Prof. Dr. Ion Chiricuta" in Cluj-Napoca, with 550 hospital beds and 25 reusable places in the day hospital, is the oldest in the country and the second-largest in Romania.

Here we present the effects of COVID-19 infection on a series of cancer patients who tested positive at our Institute until 1 February 2021.

PATIENTS AND METHODOLOGY

Study population

Nasopharyngeal samples from patients examined in our Institution between 1 April 2020 and 1 February 2021 (during the first two waves of the pandemic and before any vaccine was available for cancer patients in Romania) were collected.

The first 21 patients were diagnosed until 13 April 2020, at the initial active screening among asymptomatic hospitalized patients. From that point on, all patients were tested at admission, and those found positive were isolated and hospitalized in dedicated COVID-19 treatment units. Those patients who had a diagnosis of malignant tumor treated in our Institution and had full clinical details of SARS-CoV-2 infection outcome were included in the present study.

SARS-CoV2 PCR analysis

Samples were collected with cotton swabs in a 3 mL viral transport medium (ViroSan Transport Medium, SaniMed, Romania) and stored at 4° C before RNA extraction. The RNA extraction procedure was performed with PureLink Viral RNA/DNA Mini Kit (#12280050, Thermo Fisher Scientific, Waltham, MA, USA), and Quick- RNA Viral Kit (#R1035, Zymo Research, Irvine, CA, USA) kits.

RT-qPCR assessment of SARS-CoV-2 was performed with EliGene COVID19 BASIC A RT Kit (#90077-RT-A, Elisabeth Pharmacon, Czech Republic), Coronavirus (COVID-19) Genesig Real-Time PCR assay (#Z-Path-COVID-19-CE, Primer Design, UK). PCR data interpretation was done according to the manufacturer's protocol. The RT-qPCR instruments used in this study were LightCycler480 and Cobas Z480 (Roche, Basel, Switzerland).

COVID-19 classification and treatment

The severity of the disease was defined as asymptomatic, mild (without pneumonia), medium (with non-severe pneumonia), and severe/ critical (severe: tachypnea with >30 breaths per minute or oxygen saturation <93% at rest or PaO2/FIO2 <300 mmHg; critical: respiratory failure requiring mechanical ventilation, shock or other organ failure that requires intensive care), according to the first WHO classification (2).

Until August 2020, all patients diagnosed with SARS-CoV2 infection were hospitalized in dedicated units, even if asymptomatic. Starting with September 2020 and the second wave of the pandemic, only symptomatic patients with moderate or severe/ critical forms were hospitalized. The others were observed in isolation at home under the supervision of the family physician. The treatment, in accordance with the national protocol in use, stated that asymptomatic patients

required no treatment or vitamin C, D, and Zinc. Mild forms received antiviral treatment with lopinavir/ritonavir, antipyretics. Moderate forms received lopinavir/ritonavir + hydroxychloroquine +/- azithromycin, antipyretics. Severe/ critical forms received antiviral treatment with remdesivir or favipiravir (if available) or lopinavir/ritonavir + hydroxychloroquine + azithromycin + corticosteroid therapy (dexamethasone), tocilizumab, +/- convalescent plasma (and IgG anti-SARS-CoV-2). The treatment of respiratory failure has been adapted to severity, with supplemental oxygen by nasal cannula or oxygen mask, continuous positive airway pressure, or mechanical ventilation. Appropriate anticoagulant therapy (prophylactic or curative) has been prescribed for obese patients at intermediate, high, or very high thromboembolic risk, with thromboembolic clinical manifestations or disseminated intravascular coagulation, as recommended. Analgesic, antipyretic or anti-inflammatory treatments (paracetamol, metamizole, or non-steroidal anti-inflammatory drugs - NSAIDs) and vitamin C, D, and Zinc supplementation have also been added where appropriate at the physician's choice.

Until August 2020, patients were discharged if apyretic, with the improvement of all other symptoms and two consecutive negative nasopharyngeal PCR SARS-CoV-2 tests, at >24 hours interval, after at least 3 days of apyrexia and >7 days from the first positive test. Starting with September 2020, patients were discharged after 10-14 days if considered clinically healed and could leave isolation after 14 days if asymptomatic. Reinfection was defined as a second positive test result more than 180 days from the initial diagnosis.

Data analysis

The main purpose of this analysis was to characterize at diagnosis the prognostic factors for a) evolution to moderate and severe/ critical forms, b) clinical worsening (defined as severe/ critical forms or death), and c) overall survival. Initially, a univariate analysis was performed to identify prognostic factors using the Chi-square test and log-rank test. In the multivariate analysis, the logistic model and the Cox model were used (3). The threshold for a significant p-value was 0.05. All patient data were anonymized, our study being in accordance with the Declaration of Helsinki.

RESULTS

In the period between 1 April 2020 and 1 February 2021, from a total of 21893 nasopharyngeal swab samples performed, 10143 unique cancer patients were analyzed in our laboratory with a SARS-CoV2 RT-PCR test, with 542 positive individual patients (test positivity rate 5.34%). This figure was significantly lower than the country-level positivity rate for the same period (730,056 positive cases out of 5,601,310 tests, 13.03%, $p<0.001$) (1). The complete data related to COVID-19 infection could be retrieved for 341 positive cancer patients, and their demographics are presented in Table 1. A subset of 2 patients had a documented reinfection with SARS-CoV2 at 7 months after the first episode with a subsequent negative RT-PCR test.

Table 1. Patients characteristics (n=341)	
	n (%)
Gender	
Female	189 (55.4)
Male	152 (44.6)
Age, median	59 (range 9-89)
Age group	

0-9	1 (0.3)
10-19	4 (1.2)
20-29	9 (2.6)
30-39	24 (7)
40-49	45 (13.2)
50-59	95 (27.9)
60-69	104 (30.5)
70-79	51 (15)
80-89	8 (2.3)
ECOG PS	
0-1	247 (72.4)
2-4	94 (27.6)
BMI, median	26 (range 13.6-46.4)
BMI group	
<20	27 (7.9)
20-30	224 (65.7)
>30	90 (26.4)
Smoking status	
Active smoker	60 (17.6)
Former smoker	70 (20.5)
Non-smoker	202 (59.2)
Unknown	9 (2.6)
Pack-years, median	25 (range 2-60)
Comorbidities	
Without comorbidities	121 (35.5)
1 comorbidity	42 (12.3)
2 comorbidities	75 (22)
>2 comorbidities	103 (30.2)
Types of comorbidities	
Arterial hypertension	125 (36.7)
Ischemic cardiac disease	57 (16.7)
Diabetes mellitus	52 (15.2)
Other cardiopathy	32 (9.4)
Deep vein thrombosis and/or pulmonary embolism	32 (9.4)
Chronic obstructive pulmonary disease	28 (8.2)
Other comorbidities	28 (8.2)
Endocrinopathies	20 (5.9)
Chronic liver disease	11 (3.2)
Bacterial co-infection	10 (2.9)
Cerebrovascular disease	8 (2.3)
Peripheral arterial disease	7 (2.1)
Chronic kidney disease	6 (1.8)
Primary tumor location	

Lung	66 (19.4)
Breast	60 (17.6)
Digestive	54 (15.8)
Gynaecological	53 (15.5)
Hematological	25 (7.3)
Genito-urinary	23 (6.7)
Skin, including melanoma	20 (5.9)
Sarcoma	11 (3.2)
Head and neck	9 (2.6)
Endocrine	9 (2.6)
Multiple primary tumors	5 (1.5)
Neuroendocrine	4 (1.2)
Central nervous system	1 (0.3)
Unknown primary tumor	1 (0.3)
Present status	
Remission	37 (10.9)
Curative setting	80 (23.5)
Advanced active disease or palliation	224 (65.7)
Treatment in the previous 3 months	
No	58 (17)
Yes	283 (83)
Chemotherapy	159 (46.6)
Targeted treatment	70 (20.5)
Surgery	53 (15.5)
Immunotherapy	41 (12)
Radiotherapy	34 (10)
Hormonal therapy	34 (10)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index.

At diagnosis, among the 341 patients, 164 (48.1%) were asymptomatic, and from the 177 (51.9%) symptomatic forms, 133 (39%) were mild, 37 (10.9%) moderate and 7 (2.1%) severe/ critical. The most common complaints were fatigue (n=152 patients, 44.6%), dry cough (n=98, 28.7%), fever (n=71, 20.8%), dyspnea (n=59, 17.3%), anosmia (n=37, 10.9%) and diarrhea (n=18, 5.3%).

During the course of the infection, 138 (40.5%) patients remained asymptomatic, while 94 (27.6%) developed a mild form, 70 (20.5%) developed a moderate form, and 39 (11.4%) developed a severe/ critical form of COVID-19, Table 2.

Table 2. Clinical evolution of COVID-19 infection

		Worst clinical state			
State at diagnosis	Total	Asymptomatic	Symptomatic mild	Symptomatic moderate	Symptomatic severe/ critical
	n (%)	n (%)	n (%)	n (%)	n (%)

Asymptomatic	164 (48%)	138 (84.1%)	13 (7.9%)	11 (6.7%)	2 (1.2%)
Symptomatic mild	133 (39%)		81 (60.9%)	43 (32.3%)	9 (6.8%)
Symptomatic moderate	37 (10.8%)			16 (43.2%)	21 (56.8%)
Symptomatic severe/ critical	7 (2%)				7 (100%)
Total	341 (100%)	138 (40.5%)	94 (27.6%)	70 (20.5%)	39 (11.4%)

The 341 patients, received the following main treatments: paracetamol (n=183, 53.7%), vitamins (n=178, 52.2%), anticoagulants (n=102, 29.9%), antibiotics (other than azithromycin, n=95, 27.9%), corticosteroids (n=71, 20.8%), hydroxychloroquine (n=70, 20.5%), azithromycin (n=60, 17.6%), lopinavir/ritonavir (n=49, 14.4%), NSAIDs (n=30, 8.8%), metamizole (n=16, 4.7%), remdesivir (n=9, 2.6%), favipiravir (n=6, 1.8%), tocilizumab (n=6, 1.8%), darunavir/ritonavir (n=5, 1,5%). No treatment was given to 62 asymptomatic patients (18.2%).

At the time of data analysis, out of the total number of COVID-19 patients, 315 (92.4%) had returned home cured of COVID-19, and 26 patients (7.6%) who developed a severe/ critical form died due to the infection. The median duration until the second negative test was 13 days [limits 7-54].

The median survival of the deceased patients was 17.5 days (range 2-60) after the RT-PCR diagnosis. Four additional patients had a cancer related-death in the 30 days after being considered healed of COVID-19.

Until 1 February 2021, coinciding with database lock, a number of 30,815 COVID-19 related deaths were recorded among a total of 1,073,713 closed cases in Romania (mortality rate 2.9%), which was significantly lower compared with the 7.6% mortality rate in our cancer patients series ($p<0.001$) (1). The overall survival curve of patients and specific cancer types after COVID-19 infection is presented in Figure 1. Subgroup analysis of overall survival is presented in Figure 2.

Analysis for moderate and severe/ critical forms

A first univariate analysis was conducted for the seriousness of the infection (asymptomatic or symptomatic mild vs. symptomatic moderate or severe/ critical form of COVID-19) presented in Table 3. Factors associated with a worse prognosis in univariate analysis were male gender, advanced active disease or palliation, older age (>65), active or former smoker, PS 2-4, a high number of comorbidities (≥3), selected individual comorbidities (diabetes mellitus, ischemic cardiac disease), hematological malignancies, lung cancer and no active cancer treatment in the previous 3 months. Specifically, asymptomatic moderate or severe/ critical form of COVID-19 developed more frequently in men vs. women (41.4% vs. 24.3%, $p<0.01$), patients with advanced active disease or palliation vs. patients in remission or treated with curative intention (38.8% vs. 18.8% $p<0.01$), patients older than 65 vs. younger patients (40.4% vs 28.5%, $p=0.03$), active or former smokers vs. non-smokers (40% vs. 27%, $p=0.01$), patients with a worse PS (2-4) vs. good PS (0-1) (58.5% vs. 21.9%, $p<0.01$), patients with ≥3 vs. 0-2 comorbidities (39.9% vs. 23.3%, $p<0.01$), patients with diabetes mellitus vs. patients without (38.1% vs. 29.1%, $p<0.01$), patients with ischemic cardiac disease vs. patients without (45.6% vs. 29.2%, $p=0.02$), patients with hematological malignancies vs. patients with solid tumors (56% vs. 30.1%, $p<0.01$), patients with

lung cancer vs. other cancers (42.4% vs. 29.5%, p=0.04). Patients without a cancer-specific treatment in the 3 months previous to COVID-19 infection developed more frequently a moderate or severe/ critical form of COVID-19 vs. patients with treatment (44.8% vs. 29.3%, p=0.02). No other prognostic factors achieved statistical significance in univariate analysis with respect to the severity of COVID-19 infection. Other analyzed factors were not significant in univariate analysis and included body mass index, presence of some comorbidities (cerebrovascular disease, peripheral arterial disease, other cardiopathy, deep vein thrombosis and/or pulmonary embolism, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, infections, endocrinopathies or other comorbidities), solid cancers as digestive, breast, gynecological, genito-urinary, skin including melanoma, individual cancer treatment methods in the previous 3 months (surgery, radiotherapy, chemotherapy, hormonal therapy, targeted molecular therapy and immunotherapy).

A first multivariate analysis was performed for the eleven factors found significant from the previous univariate analysis. The factors with an independent prognostic value in the multivariate analysis were ECOG PS (HR 3.82, 95% CI 2.11-6.91 for ECOG PS 2-4, p<0.0001) and if a previous cancer treatment was given in the 3 previous months (HR 0.48, 95% CI 0.25-0.94 for treatment given, p=0.031).

Analysis for clinical worsening

A second univariate analysis was performed for clinical worsening during COVID-19 infection. Clinical worsening was defined as patients who developed a severe/ critical form or died due to COVID-19 infection. Factors with a significant negative prognosis in univariate analysis in relation to clinical worsening were male gender, advanced active disease or palliation, PS 2-4, selected individual comorbidities (diabetes mellitus, peripheral arterial disease, chronic liver disease), hematological malignancies, and no surgical treatment in the last 3 months, while breast cancer diagnosis had less clinical worsening. Specifically, a symptomatic severe/ critical form of COVID-19 or death occurred more frequently in men vs. women (17.1% vs. 6.9%, p<0.01), patients with advanced active disease or palliation vs. patients in remission or treated with curative intention (16.1% vs. 2.6% p<0.01), patients with a worse PS (2-4) vs. good PS (0-1) (36.2% vs. 2%, p<0.01), patients with diabetes mellitus vs. patients without (25% vs. 9%, p<0.01), patients with peripheral arterial disease vs. patients without (42.9% vs. 10.8%, p=0.04), patients with chronic liver disease vs. patients without (36.4% vs. 10.6%, p=0.04), patients with hematological malignancies vs. patients with solid tumors (32% vs. 9.8%, p<0.01). Patients without surgical treatment in the 3 months previous to COVID-19 infection developed more frequently a severe/ critical form of COVID-19 or died vs. patients with surgical treatment (13.2% vs. 1.9%, p=0.02). Breast cancer diagnosis vs. other cancer diagnosis was associated with less clinical worsening (1.7% vs. 13.5%, p<0.01).

A second multivariate analysis related to clinical worsening during COVID-19 infection was performed and included the nine factors identified in the univariate analysis. The multivariate analysis retained three independent prognostic factors: ECOG PS (HR 34.1, 95% CI 9.18-126.49 for PS 2-4, p<0.0001), peripheral arterial disease (HR 9.7, 95% CI 1.25-75.34 for the presence of disease, p=0.03) and chronic liver disease (HR 6.48, 95% CI 1.06-39.65 for the presence of disease, p=0.04), Table 3.

Analysis for overall survival

A third univariate analysis was performed for overall survival after COVID-19 infection. Factors significantly related to a worse overall survival at 90 days following COVID-19 infection were male vs. female gender (89% vs. 95%, p=0.03), advanced active disease or palliation vs. remission or curative setting (88% vs. 100%, p<0.01), age >65 vs. ≤65 years (88% vs. 94%, p=0.04), patients with a worse PS (2-4) vs. good PS (0-1) (73% vs. 100%, p<0.01), patients with diabetes mellitus vs. patients without (83% vs. 94%, p<0.01), patients with ischemic cardiac disease vs. patients without (86% vs. 94%, p=0.04), patients with chronic obstructive pulmonary disease vs. patients without (82% vs. 93%, p=0.02), patients with chronic liver disease vs. patients without (64% vs. 93%, p<0.01), patients with digestive tumors vs. patients with other tumors (85% vs. 94%, p=0.03) and patients with radiotherapy treatment given in the last 3 months vs. patients without (83% vs. 92%, p<0.01).

A third multivariate analysis was performed and included the ten factors from the univariate analysis. The multivariate analysis retained four independent prognostic factors: ECOG PS (HR 82.56, 95% CI 11.26-605.24 for PS 2-4, p<0.0001), ischemic cardiac disease (HR 3.05, 95% CI 1.28-7.3 for the presence of disease, p<0.0126), chronic liver disease (HR 6.85, 95% CI 2.19-21.38 for the presence of disease, p<0.001) as comorbidities associated with a negative prognosis together with radiotherapy treatment in the last 3 months (HR 4.34, 95% CI 1.67-11.28 for having radiotherapy, p=0.0027), Table 3.

Table 3. Univariate and multivariate analysis of prognostic factors associated with COVID-19 severity and survival

		Asymptomatic or symptomatic mild (A) vs. symptomatic moderate or severe/ critical (B) COVID-19					Clinical worsening: Asymptomatic or symptomatic mild/moderate (C) vs. symptomatic severe/ critical or death (D)					Overall survival at 90 days (E)				
Category	Prognostic factor	A	B	Univariate analysis	Multivariate analysis		C	D	Univariate analysis	Multivariate analysis		E	Survival	Univariate analysis	Multivariate analysis	
		n (%)	n (%)	p	OR (95% CI)	p	n (%)	n (%)	p	OR (95% CI)	p	n (%)	%	p	OR (95% CI)	p
Gender	Female	143 (75.7%)	46 (24.3%)	<0.01	1.27 (0.71-2.28)	0.43	176 (93.1%)	13 (6.9%)	<0.01	1.87 (0.76-4.61)	0.17	189 (55.4%)	95	0.03		
	Male	89 (58.6%)	63 (41.4%)				126 (82.9%)	26 (17.1%)				152 (44.6%)	89			
Present status	Advanced active disease/ palliation	137 (61.2%)	87 (38.8%)	<0.01	1.3 (0.68-2.49)	0.42	188 (83.9%)	36 (16.1%)	<0.01	0.48 (0.09-2.53)	0.39	224 (65.7%)	88	<0.01		
	Remission/ curative setting	95 (81.2%)	22 (18.8%)				114 (97.4%)	3 (2.6%)				117 (34.3%)	100			
Age	≤65	173 (71.5%)	69 (28.5%)	0.03	1.34 (0.75-2.4)	0.33	219 (90.5%)	23 (9.5%)	0.08			242 (71%)	94	0.04		
	>65	59 (59.6%)	40 (40.4%)				83 (83.8%)	16 (16.2%)				99 (29%)	88			
Smoking status	Active / former smoker	78 (60%)	52 (40%)	0.01	1.48 (0.81-2.72)	0.21	112 (86.2%)	18 (13.8%)	0.21			130 (38.1%)	92	0.65		
	Non-smoker	154 (73%)	57 (27%)				183 (90.6%)	19 (9.4%)				202 (59.2%)	93			
ECOG PS	0-1	193 (78.1%)	54 (21.9%)	<0.01	3.82 (2.11-6.91)	<0.0001	242 (98%)	5 (2%)	<0.01	34.1 (9.18-126.49)	<0.0001	247 (72.4%)	100	<0.01	82.56 (11.26-605.24)	<0.0001
	2-4	39 (41.5%)	55 (58.5%)				60 (63.8%)	34 (36.2%)				94 (27.6%)	73			
BMI	<30	166 (66.1%)	85 (33.9%)	0.21			219 (87.3%)	32 (12.7%)	0.2			251 (73.6%)	92	0.4		
	≥30	66 (73.3%)	24 (16.7%)				83 (92.2%)	7 (7.8%)				90 (26.4%)	94			
Co-morbidities	0-2	125 (76.7%)	38 (23.3%)	<0.01	1.28 (0.71-2.32)	0.41	147 (90.2%)	16 (9.8%)	0.37			163 (47.8%)	94	0.31		
	≥3	107 (60.1%)	71 (39.9%)				155 (87.1%)	23 (12.9%)				178 (52.2%)	91			
Arterial hypertension	yes	81 (64.8%)	44 (35.2%)	0.33			112 (89.6%)	13 (10.4%)	0.65			125 (36.7%)	92	0.83		
	no	151 (69.9%)	65 (30.1%)				190 (88%)	26 (12%)				216 (63.3%)	93			
Diabetes mellitus	yes	27 (51.9%)	25 (48.1%)	<0.01	1.41 (0.7-2.86)	0.34	39 (75%)	13 (25%)	<0.01	2.17 (0.84-5.61)	0.11	52 (15.2%)	83	<0.01		
	no	205 (70.9%)	84 (29.1%)				263 (91%)	26 (9%)				289 (84.8%)	94			
Ischemic cardiac disease	yes	31 (54.4%)	26 (45.6%)	0.02	1.73 (0.83-3.58)	0.14	48 (84.2%)	9 (15.8%)	0.26			57 (16.7%)	86	0.04	3.05 (1.28-7.3)	0.0126
	no	201 (70.8%)	83 (29.2%)				254 (89.4%)	30 (10.6%)				284 (83.3%)	94			
Cerebrovascular disease	yes	4 (50%)	4 (50%)	0.47			7 (87.5%)	1 (12.5%)	0.64			8 (2.3%)	88	0.6		

	no	228 (68.5%)	105 (31.5%)				295 (88.6%)	38 (11.4%)				333 (97.7%)	92			
Peripheral arterial disease	yes	3 (42.9%)	4 (57.1%)	0.3			4 (57.1%)	3 (42.9%)	0.04	9.7 (1.25-75.34)	0.03	7 (2.1%)	86	0.53		
	no	229 (68.6%)	105 (31.4%)				298 (89.2%)	36 (10.8%)				334 (97.9%)	93			
Other cardiopathy	yes	18 (56.2%)	14 (43.8%)	0.13			27 (84.4%)	5 (15.6%)	0.62			32 (9.4%)	88	0.26		
	no	214 (69.3%)	95 (30.7%)				275 (89%)	34 (11%)				309 (90.6%)	93			
Deep vein thrombosis and/or pulmonary embolism	yes	17 (53.1%)	15 (46.9%)	0.06			28 (87.5%)	4 (12.5%)	0.93			32 (9.4%)	88	0.25		
	no	215 (69.6%)	94 (30.4%)				274 (88.7%)	35 (11.3%)				309 (90.6%)	93			
Chronic obstructive pulmonary disease	yes	15 (53.6%)	13 (46.4%)	0.09			23 (82.1%)	5 (17.9%)	0.42			28 (8.2%)	82	0.02		
	no	216 (69.3%)	96 (30.7%)				279 (89.1%)	34 (10.9%)				313 (91.8%)	93			
Chronic kidney disease	yes	2 (33.3%)	4 (66.7%)	0.16			4 (66.7%)	2 (33.3%)	0.29			6 (1.8%)	83	0.41		
	no	230 (68.7%)	105 (31.3%)				298 (89%)	37 (11%)				335 (98.2%)	93			
Chronic liver disease	yes	5 (45.5%)	6 (54.5%)	0.19			7 (63.6%)	4 (36.4%)	0.03	6.48 (1.06-39.65)	0.04	11 (3.2%)	64	<0.01	6.85 (2.19-21.38)	0.001
	no	227 (68.8%)	103 (31.2%)				295 (89.4%)	35 (10.6%)				330 (96.8%)	93			
Infections	yes	5 (50%)	5 (50%)	0.37			7 (70%)	3 (30%)	0.17			10 (2.9%)	80	0.12		
	no	227 (68.6%)	104 (31.4%)				295 (89.1%)	36 (10.9%)				331 (97.1%)	93			
Endocrinopathies	yes	17 (85%)	3 (15%)	0.09			19 (95%)	1 (5%)	0.57			20 (5.9%)	95	0.65		
	no	215 (67%)	106 (33%)				283 (88.2%)	38 (11.8%)				321 (94.1%)	92			
Other co-morbidities	yes	19 (67.9%)	9 (32.1%)	0.98			27 (96.4%)	1 (3.6%)	0.29			28 (8.2%)	100	0.12		
	no	213 (68.1%)	100 (31.9%)				275 (87.9%)	38 (12.1%)				313 (91.8%)	92			
Tumor type	Hematological	11 (44%)	14 (56%)	<0.01	2.64 (0.97-7.15)	0.057	17 (68%)	8 (32%)	<0.01	1.88 (0.61-5.88)	0.27	25 (7.3%)	84	0.11		
	Solid tumors	221 (69.9%)	95 (30.1%)				285 (90.2%)	31 (9.8%)				316 (92.7%)	93			
Lung	yes	38 (57.6%)	28 (42.4%)	0.04	1.36 (0.68-2.74)	0.39	58 (87.9%)	8 (12.1%)	0.85			66 (19.4%)	92	0.99		
	no	194 (70.5%	81 (29.5%)				244 (88.7%)	31 (11.3%)				275 (80.6%)	92			
Digestive	yes	33 (61.1%)	21 (38.9%)	0.23			44 (81.5%)	10 (18.5%)	0.07			54 (15.8%)	85	0.03		
	no	199 (69.3%)	88 (30.7%)				258 (89.9%)	29 (10.1%)				287 (84.2%)	94			

Breast	yes	47 (78.3%)	13 (21.7%)	0.06			59 (98.3%)	1 (1.7%)	<0.01	0.41 (0.04-3.82)	0.44	60 (17.6%)	98	0.06		
	no	185 (65.8%)	96 (34.2%)				243 (86.5%)	38 (13.5%)				281 (82.4%)	91			
Gynecological	yes	40 (75.5%)	13 (24.5%)	0.21			46 (86.8%)	7 (13.2%)	0.66			53 (15.5%)	89	0.26		
	no	192 (66.7%)	96 (33.3%)				256 (88.9%)	32 (11.1%)				288 (84.5%)	93			
Genito-urinary	yes	13 (56.5%)	10 (43.5%)	0.22			21 (91.3%)	2 (8.7%)	0.93			23 (6.7%)	96	0.55		
	no	219 (68.9%)	99 (31.1%)				281 (88.4%)	37 (11.6%)				318 (93.3%)	92			
Skin, including melanoma	yes	17 (85%)	3 (15%)	0.09			20 (100%)		0.33			20 (5.9%)	100	0.19		
	no	215 (67%)	106 (33%)				282 (87.9%)	39 (12.1%)				321 (94.1%)	92			
Treatment in the previous 3 months	yes	200 (70.7%)	83 (29.3%)	0.02	0.48 (0.25-0.94)	0.031	253 (89.4%)	30 (10.6%)	0.28			58 (17%)	93	0.83		
	no	32 (55.2%)	26 (44.8%)				49 (84.5%)	9 (15.5%)				283 (83%)	92			
Surgery	yes	40 (75.5%)	13 (24.5%)	0.21			52 (98.1%)	1 (1.9%)	0.02	0.13 (0.02-1.15)	0.07	53 (15.5%)	98	0.09		
	no	192 (66.7%)	96 (33.3%)				250 (86.8%)	38 (13.2%)				288 (84.5%)	91			
Chemo-therapy	yes	108 (67.9%)	51 (32.1%)	0.97			138 (86.8%)	21 (13.2%)	0.34			159 (46.6%)	91	0.25		
	no	124 (68.1%)	58 (31.9%)				164 (90.1%)	18 (9.9%)				182 (53.4%)	94			
Radio-therapy	yes	25 (73.5%)	9 (26.5%)	0.47			28 (82.4%)	6 (17.6%)	0.36			34 (10%)	82	0.01	4.34 (1.67-11.28)	0.0027
	no	207 (67.4%)	100 (32.6%)				274 (89.3%)	33 (10.7%)				307 (90%)	93			
Hormonal therapy	yes	26 (76.5%)	8 (23.5%)	0.27			33 (97.1%)	1 (2.9%)	0.17			34 (10%)	97	0.28		
	no	206 (67.1%)	101 (32.9%)				269 (87.6%)	38 (12.4%)				307 (90%)	92			
Targeted therapy	yes	49 (70%)	21 (30%)	0.69			63 (90%)	7 (10%)	0.67			70 (20.5%)	94	0.49		
	no	183 (67.5%)	88 (32.5%)				239 (88.2%)	32 (11.8%)				271 (79.5%)	92			
Immuno-therapy	yes	31 (75.6%)	10 (24.4%)	0.27			38 (92.7%)	3 (7.3%)	0.53			41 (12%)	95	0.49		
	no	201 (67%)	99 (33%)				264 (88%)	36 (12%)				300 (88%)	92			

ECOG PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index.

DISCUSSION

The Oncology Institute "Prof. Dr. Ion Chiricuta" from Cluj-Napoca has been significantly affected by the COVID-19 pandemic, however, sustained measures have been taken to counteract the disruption of activity through bimonthly PCR screening of all staff, PCR screening of patients with symptoms suggestive for COVID-19 infection, PCR screening of asymptomatic patients prior to inpatient care, surgical or interventional radiology procedures, radiotherapy sessions or systemic therapy (chemotherapy, immunotherapy, targeted therapy), creation of COVID-19 free pathways and treatment spaces, regular staff and patient information on the correct use of protective equipment.

Analysis of our series of patients infected with COVID-19 showed that the incidence among cancer patients was lower than the national incidence. This finding could be explained by the more active prophylactic measures taken by cancer patients (self-isolation, social distancing, mask-wearing, washing hands) who by all means try to avoid COVID-19 infection due to the risks of a more severe evolution and the interference with the anticancer treatments. The higher positivity rate of the national incidence could also be explained by the strict selection criteria for cases tested at the national level, according to the National Institute for Public Health methodology. At a national level, most tests were performed on suspect symptomatic cases, according to the case definition, while in our Institute most cases tested were asymptomatic, and were scheduled for inpatient care or oncological treatments. Active screening with nasopharyngeal PCR was used to screen for SARS-CoV-2 in the asymptomatic phase in almost half of the cases (48%). At the time of diagnosis, 51.9% had one or more symptoms: fatigue, dry cough, fever, dyspnea, anosmia/ ageusia, or diarrhea.

Confirming the results reported by Chinese and Italian authors (4-8) and not in line with the initial results from the Gustave Roussy Institute (9), in our series the mortality rate for the closed cases of COVID-19 in patients with cancer was significantly higher compared to the general population in Romania (7.6% vs. 2.9%, $p<0.01$, RR=2.7). These local results can constitute a quantitative argument for Romanian doctors to recommend vaccination as an efficient weapon to transform COVID-19 into a preventable disease for their cancer patient population. None of the patients included in the present analysis were vaccinated, given that the vaccination program for oncological patients started on 1 February 2021 in Romania.

In univariate analysis, in our series, the factors with a pejorative prognosis related both to a moderate or severe/ critical evolution of COVID-19 infection, clinical worsening (severe/ critical form and/or death), and an impaired survival with COVID-19 infection were male gender, advanced active cancer, a declined PS (2-4), and presence of diabetes as an individual comorbidity.

We identified additional factors that were predictive for a moderate or severe/ critical evolution of COVID-19 infection such as age over 65, active or former smoker, more than 3 comorbidities, ischemic cardiac disease, hematological malignancies, lung cancer, and no specific cancer treatment in the previous three months.

Factors that were predictive for clinical worsening of COVID-19 infection included peripheral arterial disease, chronic liver disease, hematological malignancies, and no specific surgical cancer treatment in the previous three months, with breast cancer having a better outcome.

Factors that were negatively correlated with survival due to COVID-19, included age over 65, ischemic cardiac disease, chronic obstructive pulmonary disease, chronic liver disease, digestive tumors, and radiotherapy in the last 3 months.

Some analyzed factors were found to have positive prognostic value in other studies (presence of obesity and certain comorbidities, surgical treatment, or chemotherapy in the previous three months), however, we found no significant positive relationship in our study.

On multivariate analysis, PS 2-4 was the only independent predictor for a moderate or severe/ critical evolution, clinical worsening, and overall survival ($p<0.0001$) due to SARS-CoV2 in our series. Additionally, the multivariate analysis highlighted other independent prognostic factors for a moderate or severe/ critical evolution of COVID-19 (absence of cancer treatment in the previous 3 months, statistical trend for the hematological malignancies), for clinical worsening (peripheral arterial disease, chronic liver disease) and for overall survival (ischemic cardiac disease, chronic liver disease, radiotherapy in the previous 3 months).

Gustave Roussy Institute reported, in a series of 137 cancer patients, a positivity rate of the RT-PCR test and mortality that were similar with the ones in the general population. Prognostic factors for clinical worsening in a univariate analysis were PS >1, hematological malignancies, cancer treatment in the last 3 months and chemotherapy in the last 3 months. Only PS remained significant for clinical worsening in a multivariate analysis. In the same series, prognostic factors for COVID-19 survival in a univariate analysis were PS, disease status (active/ metastatic) and chemotherapy treatment in the last 3 months. Again, only PS remained significant for survival in the multivariate analysis(9).

In a multicenter cohort study in the province of Hubei, China, 105 COVID-19 patients with cancer were compared with 653 COVID-19 patients without cancer. Patients with cancer appeared significantly more vulnerable to SARS-CoV-2 (at 3.5 times the risk compared to the general population in terms of necessity of invasive ventilation, admission to ICU, severe/ critical forms, and death (10). The fatality rate for infected cancer patients in China is 28.6% (11), compared to a 2.3% fatality rate for all COVID-19 patients (12). The major risk factor for cancer patients during the COVID-19 pandemic is their inability to receive enough medical care (13).

The largest international registry of patients with thoracic tumors and COVID-19 infection called TERAVOLT included 1012 patients from 20 countries (Europe 74% and North America 23%) and found a very high mortality for this category of patients (32%). Patients presenting with pneumonia (OR 2.7), consolidation (OR 2), bilateral involvement of the lungs (OR 2.8), and pleural effusion (OR 2.7) had a higher risk of death. In multivariate analysis, the factors significantly related to a fatal evolution of COVID-19 infection were PS ≥2 (OR 3.7), stage IV (OR 1.9), active smoker or ex-smoker status (OR 2), corticosteroids use before the diagnosis of COVID-19 (OR 1.8), age over 65 years (OR 1.5). Chemotherapy and targeted molecular therapy were not correlated to a higher risk of death and immunotherapy had a lower risk of mortality (OR 0.6) (14).

Based on these results, the authors developed a nomogram that predicts mortality in patients with chest tumors and COVID-19. Patients receive a score based on ECOG PS, stage, smoking/ non-smoking status, age, steroid use, and the type of systemic treatment. For example, a 70-year-old smoker with an ECOG 2 PS who received third-line chemotherapy with docetaxel for a stage IV squamous carcinoma has a score of 260 that translates into a risk of death of over 60%. A 50-year-old non-smoker with an ECOG 0 who receives first-line therapy with osimertinib for a Stage IV NSCLC has a score of 55 points, which translates into a lower risk of death of 20%.

Zhang et al. studied the outcomes of cancer patients with COVID-19 and found more than fourfold higher likelihood of experiencing severe events in those who received therapy in the preceding 14 days of COVID-19 diagnosis (11).

To assist healthcare facilities, leading oncology societies such as the European Society of Medical Oncology, the American Society of Clinical Oncology, National Comprehensive Cancer Network have developed guidelines to mitigate the negative effects of the COVID-19 pandemic on the diagnosis and treatment of cancer patients (15-17).

The drugs used in >50% of patients were paracetamol and vitamins and in 20%-30% anticoagulants, antibiotics, hydroxychloroquine. Among the approved drugs for SARS-CoV-2, corticoids, authorized in the severe forms following the RECOVERY study (18, 19), were used in 20.8% of patients in our series. Other authorized medications, the antiviral agent remdesivir and also the monoclonal anti-IL6 antibody tocilizumab (20-23), considered active in the severe/ critical forms, and convalescent plasma transfusion were administered in <5% of the patients. No anti-SARS-CoV-2 therapeutic antibodies and no vaccines were available in the studied period. The number of patients treated with each drug and the retrospective nature of the study does not support any conclusions about their effectiveness.

Conclusion

Although the COVID-19 pandemic has posed obstacles to the conduct of the activity at the Oncology Institute "Prof. Dr. Ion Chiricuta", the introduction of protective measures and systematic screening of the virus for the staff and patients (before inpatient treatment and major diagnostic and therapeutic procedures), were implemented in an effort to keep the Institute virus-free with a dedicated buffer department.

In our series the mortality of COVID-19 infection appeared to be greater among cancer patients compared with the general population.

Performance status was the only independent prognostic factor found in all our multiple multivariate analysis, related both to an evolution towards a moderate or severe/ critical form, to clinical worsening and to an impaired survival with COVID-19.

FUNDING

This work was supported by the Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca [grant number 4556/01.10.2020].

DISCLOSURE

ACP reports personal fees from ROCHE, MERCK SERONO, SANDOZ, support for attending meetings and/or travel from ACCORD, PFIZER, grants from University of Medicine and Pharmacy Iuliu Hatieganu Cluj-Napoca, outside the submitted work. TC reports personal fees from ASTELAS PHARMA, JANSSEN, MERCK SHARP & DOHME, MERCK SERONO, AMGEN, ROCHE, PFIZER, SANOFI GENZYME, SERVIER, IPSEN, ASTRA ZENECA, LILLY, NOVARTIS, BOERIGHER INGELHEIM, BRISTOL MYERS SQUIBB, grants from University of Medicine and Pharmacy Iuliu Hatieganu Cluj-Napoca, outside the submitted work. PK reports personal fees from ROCHE, SANDOZ, BRISTOL MYERS SQUIBB, ASTRAZENECA, MERCK SERONO, PPROEVENTS, ASTELLAS PHARMA, support for attending meetings

and/or travel from SANDOZ, ELLI LILLY, ROCHE, BOEHRINGER INGELHEIM, grants from University of Medicine and Pharmacy Iuliu Hatieganu Cluj-Napoca, Romanian National Authority for Scientific Research, COST Association, outside the submitted work. CM reports support for attending meetings and/or travel from ROCHE, PFIZER, ACCORD, outside the submitted work. MBV reports support for attending meetings and/or travel from ROCHE, PFIZER, ACCORD, SERVIER, outside the submitted work. CV reports grants from Romanian National Authority for Scientific Research, COST Association, outside the submitted work. All other authors have nothing to declare.

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